THE CLINICAL SIGNIFICANCE OF FASCICULATIONS IN VOLUNTARY MUSCLE

BY

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Spontaneous twitching of the voluntary muscles has aroused the interest of clinicians and neurophysiologists for many years. Despite the classical paper of Denny-Brown and Pennybacker in 1938, and other valuable though less well-known contributions by Ayer *et al.* (1934), Ford (1939), Odom *et al.* (1943), Denny-Brown and Foley (1948), and the earlier observations of Duchenne (1855), of Kny (1888), and of Schultze (1894) on myokymia, the view is still widely held, both in the United States and in Great Britain, that such spontaneous involuntary flickering, if it occurs repeatedly in muscles other than those of the eyelids or periorbital area, and particularly if it occurs in the small muscles of the hand, is indicative of progressive muscular atrophy (P.M.A.).

The terms " fasciculation " and " fibrillation " are still sometimes used synonymously to describe these visible twitchings, and their appearance in the hands, arms, or feet of doctors or medical students may strike terror into these patients' hearts, whereas in the layman the phenomenon may be scarcely noticed, and even if observed is unlikely to provoke alarm in the absence of other complaint. During the past five years we have collected 16 cases, of which no fewer than 10 were in doctors or senior medical students. In all these cases spontaneous fasciculation was occurring repeatedly and was often widespread, and none were in fact suffering from P.M.A. It is of some interest, however, that in every one of the 10 medically trained patients the presenting complaint was of fasciculation, and the overwhelming anxiety thereby aroused concerning the possible diagnosis dominated the picture, whereas the presence of fasciculation had been noticed subjectively by only one of the six non-medical patients.

It has seemed worthwhile to record our observations on this group if only to clarify further a benign syndrome already described, but still apparently too little known to prevent considerable unnecessary distress and apprehension.

The Problem

Our first concern was to identify, measure, and record true fasciculations, as distinct from fibrillation, and to correlate these records with clinical diagnosis. We accepted, and were able subsequently to confirm, the clear differentiation made by Denny-Brown and Pennybacker between these terms. Fasciculations are the gross visible and often palpable and subjectively sensible contractions of a number of muscle fibres supplied by a single motor-nerve filament; in other words, contractions of motor units. Whereas the motor unit is a physiological whole, a fasciculus or muscle bundle is composed of a number of separate motor units loosely knit together on a purely anatomical basis. Clinical fasciculation can involve part or all of a fasciculus—that is, from one to all of its motor units. We were interested in the possible correlation between the extent and duration of such fasciculation and its significance in clinical terms. On the electromyograph the duration of fasciculation varies between 8 and 12 milliseconds, its amplitude between 0.5 and 1 millivolt.

Fibrillation, on the other hand, is produced by the contraction of individual muscle fibres no longer under the control of a motor nerve: it is seen only in conditions involving severance or degeneration of the nerve supply. Such individual contractions are so small that although hundreds are probably occurring together at any one instant, they remain invisible under ordinary skin. In the tongue, however, they can be seen by the aid of a lens and careful lighting. On the electromyograph they last 0.5 to 1 millisecond and are no more than 30 to 60 microvolts in amplitude. They are not usually recordable on an ink-writing oscillograph, requiring special electromyographic techniques with the use of needle electrodes and a cathode-ray screen for their demonstration, though we were able to overcome this difficulty without needle electrodes for clinical purposes, as will be seen. The problem here was to record both fibrillation and fasciculation at the same time if both were present, and again to correlate this with the clinical state.

Method

The normal full clinical history and examination of the nervous system formed the basis of our approach to patients: the mental state and psychiatric history were carefully evaluated. Subsequent follow-up extended from a minimum of seven months to a maximum of six years from the time when the fasciculations were first observed.

Electromyographic studies were made with surface electrodes and an ink-writing oscillograph, storing the electromyographic discharge on to a wire recorder and playing it back at one-fifth normal speed into the ink-writer when the presence or absence of fibrillation was under investigation. The findings in the 16 benign cases were compared with a number of established cases of progressive muscular atrophy or amyotrophic lateral sclerosis.

Results

As has already been stated, all 16 cases forming the subject of this report displayed continuous and often widespread fasciculations; none suffered from any form of P.M.A. The medical patients showed a number of features in common: in nine out of ten the fasciculations had occurred in the small muscles of the hands as well as elsewhere, and had been accompanied by tension, anxiety, fatigue, and some insomnia. In complaining of this the patients stressed their own conviction that their undeniable tension and distress were secondary to apprehension of the diagnosis of P.M.A., with all that this implied: but in every case objective consideration of their recently preceding history and situation revealed other and important sources of emotional disturbance.

In every case the fasciculations had been noticed by the doctor or student concerned and had been a source of great anxiety and misery for some weeks or months before he had been able to bring himself to seek the advice of a colleague. In several cases an electromyographic examination with an ominous or equivocal report—for example, " diphasic spontaneous action potentials . . . consistent with P.M.A."—had added to the

patient's tribulation before the diagnosis had been questioned or the case came under our observation.

With the exception of a case (No. 4) in which there was radiological evidence of arthritis of the cervical spine, none of the medical patients displayed any evidence of structural abnormality, nor of weakness or wasting, whatever. Apart from the fasciculations their clinical picture included the tension, apprehension, and anxiety already mentioned, a tendency to cramps and hyperhidrosis especially of the palms and axillae, some loss of appetite, disturbance of sleep, and tremor of the outstretched hands. They displayed, in fact, the classical syndrome of myokymia as originally described by Kny and by Schultze.

One only of the non-medical group of six patients complained primarily of fasciculation. He was a 36-year-old university professor (Case 13, below). By the time we saw him the ominously guarded nature of the medical opinions he had received, reinforced by his own amateur but highly intelligent researches into the medical literature, had reduced him to a state of iatrogenic alarm and despondency comparable to that of his medical fellow-sufferers. Like them, his was a case of myokymia. The other five patients included four women between the ages of 26 and 40 currently under treatment for anxiety state or mixed affective disorder at the Department of Psychiatry of the Massachusetts General Hospital, and a young man of 22, an engineer, who actually had muscular dystrophy of the distal type described by Gowers. Three brief illustrative case histories are appended.

Illustrative Cases

Case 2.—A 22-year-old medical student noted fasciculations in the small muscles of the left hand. Six months later he noted the same thing in the right hand during the writing of an examination. He made the diagnosis of P.M.A. himself and came to us for an electromyogram. Neurological examination disclosed no abnormality, nor was there any sign of weakness or wasting whatever. Fasciculations could be elicited from both hands after gentle tapping. The electromyogram revealed these fasciculations as coarse and of maximal duration, involving a number of motor units in the fasciculi concerned, and unaccompanied by fibrillation. These are the findings in myokymia. In view of this, and the length and nature of the history in the absence of evidence of atrophy, he was firmly reassured. It is now over a year since he consulted us, and he has had no further trouble.

Case 7.—For about four years a 41-year-old surgeon had noted fasciculations intermittently in the abductor pollicis and adductor digiti quinti of the right hand, particularly during long operations. He happened to see a case of P.M.A. discussed at "grand rounds" and became so afraid that he might have the same disease that, rather informally, he consulted a colleague, who looked at his hands and said that he might well have it. He spent about three months in a state of utter misery and despair, convinced that his days were numbered and waiting for the inevitable atrophy and difficulty in swallowing to appear. Finally he consulted one of us (R. S. S.). Examination showed no neurological changes; there were occasional fasciculations in the intrinsic muscles of both hands, slight tremor of the extended fingers, and some sweating in both hands. The patient stated that when the fasciculations appeared he also felt some discomfort and a "sense of uselessness" in his hands. He is a tense, exceptionally meticulous operator who undoubtedly suffers considerable strain and anxiety during surgical procedures. He was immensely relieved to learn that he did not have P.M.A., and a year later stated that his fasciculations hardly bothered him at all and his morale had entirely changed.

Case 13.—A 36-year-old university professor first noticed fasciculation in the muscles of his right hand following prolonged writing three years before coming under our observation. He was at this time overseas with the U.S. Army. A civilian physician in the area proffered the diagnosis of "creeping paralysis" and set the stage for a long-continued state of anxiety and apprehension. Fasciculations were intermittent, sometimes a month going by without their appearance. Eighteen months later he consulted another physician, who found no atrophy but noted the visible fasciculations, which at times were brisk enough to move a finger. The remainder of the neurological examination was normal. To settle the diagnosis, the doctor ordered an electromyogram of the muscles, putting on the referral slip, "? possibility of P.M.A." The report read: "Diphasic spontaneous action potentials seen in the muscles of the calf and occasionally in the abductor digiti quinti. Consistent with the diagnosis of P.M.A." On the strength of this the diagnosis of P.M.A. was accepted, but eventually a further electromyographic investigation was requested, and in this way he came to us. By this time it was perfectly apparent that he was not suffering from P.M.A., there being no atrophy despite the occasional fasciculations, nor any abnormal neurological findings. He recovered his morale with appropriate reassurance and has remained well.

Electromyographic Studies

The nature of these has already been indicated. They are further illustrated by Figs. 1, 2, and 3. While the simultaneous occurrence of fibrillation and fasciculation

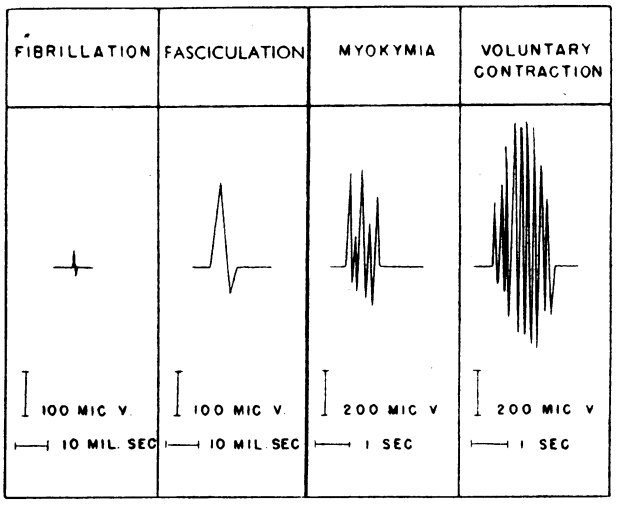

FIG. 1.—Diagrammatic relationship of a fibrillation to a fasciculation and the relationship of myokymia to a voluntary contraction. Note that fibrillation lasts for approximately 1 millisecond and is of low amplitude, whereas the fasciculation lasts for 10 milliseconds and is three to four times the amplitude of the fibrillation. The myokymia is of a shorter duration and lesser amplitude than the voluntary contraction.

in a record must undoubtedly suggest active degeneration, fasciculations by themselves carry no such ominous significance. Furthermore, our clinical impression, based on the modest number of cases at our disposal, tends to confirm the earlier view of Denny-Brown and Pennybacker that the benign fasciculations of myokymia are measurably different from those associated with progressive atrophy; the former being comparatively gross, coarse, and slow and involving most or all of the motor units in a fasciculus, while the latter are more apt to be confined to a small portion of the fasciculus, perhaps a single motor unit, and to be briefer in duration and more rapid in oscillation.

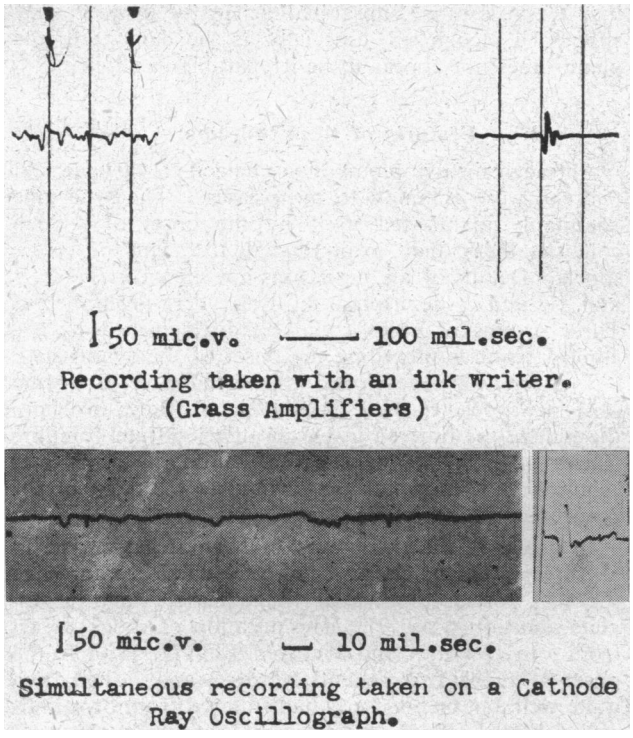

FIG. 2.—This shows the appearance of a fasciculation on an ink-writing oscillograph, and at the bottom part of the picture the same fasciculation is shown in a cathode-ray photograph (right of picture); whereas the fibrillations are indistinguishable on the ink-writer, they show up clearly on the cathode-ray screen.

The use of surface electrodes and a wire recorder to test for fibrillation (Fig. 3) is naturally preferable to needle electrodes for patients who are already anguished and apprehensive.

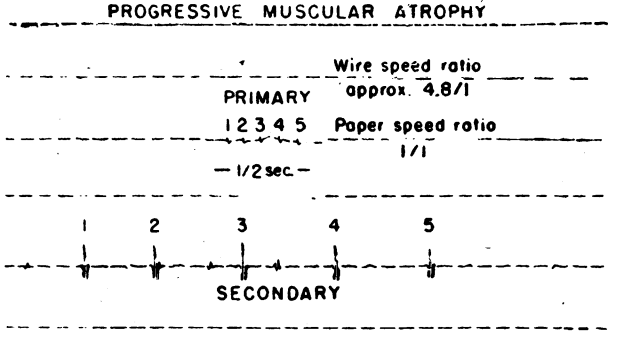

FIG. 3.—By storing the electromyographic discharge on a wire recorder and playing it back at one-fifth the speed into an ink-writer, it is possible to pick up fibrillation without the use of needle electrodes. The third line shows the ordinary recording from a patient with progressive muscular atrophy on an ink-writing oscillograph. Five fasciculations were recorded and are numbered under the word "primary." In the fifth line these same discharges were recorded on the same ink-writer after having been stored in the wire and fed back at one-fifth the speed. The five fasciculations are seen under their numbers, but in addition there are three fibrillations—one before 1, one between 2 and 3, and one between 3 and 4—that were invisible with the ordinary ink-writing technique but were brought out by this method.

Discussion

The occurrence of fasciculations in conditions other than progressive muscular atrophy—for example, thyrotoxic myopathy—is of course widely recognized (Ayer *et al.*, 1934; Starling, *et al.*, 1938; Bartels and Pizer, 1944), although their appearance or exacerbation as a manifestation of emotional tension alone, without any other pathological significance, would seem less well known. While the cause of fibrillation is considered by Denny-Brown and Pennybacker to be an increase in the sensitivity of denervated muscle to normally present acetylcholine, that of fasciculation has been postulated both as a peripheral enhancement of the cholinergic transmitting mechanism at the myoneural junction and a disordered or excessive liberation of acetylcholine at this junction. Odom *et al.* (1943) have even suggested that this local peripheral phenomenon may eventually damage the anterior horn cells and predispose to their degeneration, quoting the findings of Maslard Wigton that antidromic impulses can be traced ascending the motor nerves after fasciculation produced by neostigmine. None the less, they refer in the same paper to a case exhibiting coarse benign and widespread fasciculations over a period of 22 years without ill effect.

Such benign fasciculation may underlie some of the reports of cure or arrest of progressive muscular atrophy by various vitamin extracts, notably vitamin B and *a*-tocopherol (Wechsler, 1940a, 1940b; Stone, 1950; and others). Several of our medical patients had been treating themselves with these preparations, and, had their fears about diagnosis been unrelieved, their subsequent freedom from progressive weakness and wasting might well have been ascribed to an arrest on this basis. Apart from the absence of fibrillation and the preponderance of comparatively coarse fasciculations on electromyography, we have adopted one further clinical criterion in assessing fasciculation as benign: this is its persistence for over three months without the appearance of measurable weakness or wasting. We base this on the observation of Nielsen (1946) that atrophy invariably follows fasciculation "very shortly"—usually within 30 days. Not all clinicians would agree with our inference, however, Odom *et al.* (1943) remarking that in some cases of P.M.A. fatigue and cramps may appear "long before" the onset of demonstrable atrophy.

In conclusion we would emphasize our view that, whereas progressive muscular atrophy or degeneration from whatever cause is a comparatively rare phenomenon, fasciculations in voluntary muscle are not at all uncommon. While they may occur in the entire absence of fatigue or stress and in some individuals are practically a lifelong phenomenon, when accompanied by cramps, sweating, tremor of the outstretched hands, some physical discomfort and emotional tension with subjective fatigue, insomnia, and disturbance of appetite, they form part of the syndrome of myokymia which, to medical patients in particular, is apt to be exceedingly alarming. Their comparatively benign significance, however, can be established by their coarseness and duration, the absence of underlying fibrillation, and their persistence without weakness or wasting of the affected muscles.

With firm reassurance and attention to the psychological and emotional stresses involved, they cease to disturb the patient, although they may never entirely disappear.

Summary

The results of electromyographic and clinical observations on 15 patients with benign fasciculations and one with a distal type of muscular dystrophy are described, and are compared with cases whose fasciculations formed an accompaniment to progressive muscular atrophy. The conclusion is reached that benign fasciculations are

comparatively common, particularly in relation to emotional stress, that they are distinguishable electromyographically from those associated with muscular degeneration, and that patients displaying them can also be differentiated clinically from patients with progressive muscular atrophy at a reasonably early stage. Attention is drawn to the liability of medically trained people to suffer considerable avoidable anxiety in the absence of such distinction being clearly made.

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ACUTE SUPRARENAL INSUFFICIENCY IN PREGNANCY

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Death in the puerperium may be due to many causes, but one of the main "obstetrical" factors is shock occurring at the time of delivery. Death may be immediate but is often delayed, and in these cases it is generally accepted that the cause is either a pituitary necrosis or uraemia due to acute renal damage. From time to time, however, cases occur in which no sign of necrosis can be found in the pituitary and the patients show no evidence of uraemia. Also, there are some patients who die during pregnancy apparently without sufficient cause.

Nine such cases have come under our notice, and in our opinion death was due to acute adrenal insufficiency. Suprarenal haemorrhages are not confined to obstetric practice. They are found in the newborn, and in cases of the Waterhouse–Friderichsen syndrome, which occurs in older children and also in adults. This syndrome consists of fulminating meningococcal septicaemia with massive purpura and bilateral suprarenal haemorrhages. They have also been reported in cases of spontaneous thrombosis of suprarenal veins apart from pregnancy. This, according to Hall and Hemken (1936), is the commonest cause of suprarenal haemorrhage in adults. They also occur in any generalized "haemorrhagic" condition.

In view of the remarkable advances being made in the synthesis of suprarenal hormones it is important that these cases of suprarenal deficiency in pregnancy should be recognized, especially as the damage to the glands does not appear to be irreparable in all cases.

Features of the Syndrome

Although the symptomatology tended to vary, certain features were common to most cases. The syndrome commonly manifested itself by the onset of sudden collapse, the patient exhibiting all the signs of severe shock. Details of the nine cases are shown in Tables I and II, and a description of Case 1 is given below. Three groups of cases could be distinguished by the clinical features preceding the onset of the syndrome: (A) those who developed the syndrome following obstetric shock (Cases 2, 3, and 7); (B) those in whom the illness was ushered in by an attack of late vomiting (Cases 1, 4, 6, and 8); and (C) those in whom pre-eclamptic toxaemia was present before the onset of the syndrome (Cases 5 and 9).

In group A the shock was of haemorrhagic type in all three cases, the causes being accidental haemorrhage (Case 2), post-partum haemorrhage (Case 3), and incomplete abortion (Case 7). The duration of shock varied from 5 to 12 hours, and averaged 9 hours. Prior to the onset of shock two patients (Cases 3 and 7) had been quite well, but one (Case 2) had suffered from bronchitis and debility. These patients recovered from the state of obstetric shock but later collapsed again.

In group B three cases had late vomiting (Cases 4, 6, and 8). The duration of the vomiting before the development of the syndrome varied from 4 to 14 days and averaged 11 days. In Case 4 the vomiting was associated with epigastric pain, and there was a previous history of gastric ulcer. There was associated pyelitis in Case 8, and pre-eclamptic toxaemia was doubtfully present in Cases 6 and 8. The vomiting in Case 1 was slight, but had been continuous throughout pregnancy.

In group C there was definite evidence of pre-eclamptic toxaemia in Cases 5 and 9, and the duration was six and eight weeks respectively. There was no other illness in the antenatal period in Case 6, but in Case 8 there was evidence of pyelonephritis at necropsy.

The syndrome was ushered in by abdominal pain in Cases 1 and 2, and by lumbar pain in Case 4. In Cases 3, 4, and 8 the presenting sign was a rigor. Exhaustion was present just before the onset of the syndrome in Case 1.

During the phase of collapse the condition of the patient was indistinguishable from that of severe shock: the pulse was rapid and weak and at times almost imperceptible; the skin was cold and clammy and the blood pressure low. In Cases 1, 3, 5, and 8 the patient was markedly cyanosed. In their subsequent progress the cases could be divided into two groups.

1. Five patients (Cases 2, 4, 5, 7, and 8) failed to rally from this stage of collapse, and their survival times varied from ½ to 12 hours. During the whole of this period they remained in the same shocked condition, gradually lapsing into coma. In Cases 2, 4, and 7 vomiting developed during the stage of collapse. These five patients did not belong to any single one of the aforementioned groups. In three of these cases there was extensive haemorrhagic destruction of the gland, the central vein was thrombosed in Case 2, and Case 5 showed numerous petechial haemorrhages and marked cellular degeneration.